2018-2097

IN THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

VALEANT PHARMACEUTICALS INTERNATIONAL, INC., SALIX PHARMACEUTICALS, INC., PROGENICS PHARMACEUTICALS, INC., WYETH LLC FKA WYETH,

Plaintiffs-Appellees,

v.

MYLAN PHARMACEUTICALS INC., MYLAN INC., MYLAN LABORATORIES LIMITED,

Defendants-Appellants,

v.

ACTAVIS LLC,

Defendant.

Appeals from the United States District Court for the District of New Jersey in Case Nos. 2:15-cv-08180-SRC-CLW, 2:15-cv-08353-SRC-CLW, 2:16-cv-00035-SRC-CLW, 2:16-cv-00889-SRC-CLW, 2:17-cv-06714-SRC-CLW. Judge Stanley R. Chesler.

PLAINTIFFS-APPELLEES' COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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Dated: June 22, 2020

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Valeant Pharmaceuticals Intl. **v.** Mylan Pharmaceuticals Inc.

Case No. 18-2097

THIRD AMENDED CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ☐ (appellant) ☐ (respondent) ■ (appellee) ☐ (amicus) ☐ (name of party)

Valeant Pharmaceuticals International, Inc., Salix Pharmaceuticals, Inc., Progenics Pharmaceuticals, Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Valeant Pharmaceuticals International, Inc.	Bausch Health Companies Inc. fka Valeant Pharmaceuticals International, Inc. (The corporate name change was effective July 13, 2018)	None
Salix Pharmaceuticals, Inc.	None	See attached.
Progenics Pharmaceuticals, Inc.	None	BlackRock Institutional Trust Company, N.A.; Altiva Management Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

M. Andrew Holtman, Megan Leinen Johns (No longer with the Firm) and Caitlin O'Connell of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.; William P. Deni, Jr., Lauren B. Cooper (No longer with the Firm) and Cymetra M. Williams of Gibbons P.C.

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

Valeant Pharmaceuticals International, Inc., et al. v. Mylan Pharmaceuticals, Inc., Civil Action No. 15-08180 (D.N.J.) (Consolidated).

10/3/2019
Date

/s/ Bryan C. Diner
Signature of counsel

Please Note: All questions must be answered

Bryan C. Diner
Printed name of counsel

cc: See attached.

Reset Fields

ATTACHMENT TO THE AMENDED CERTIFICATE OF INTEREST

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Salix Pharmaceuticals, Inc.	None	Salix Pharmaceuticals, Ltd. is a wholly-owned direct subsidiary of VRX Holdco. VRX Holdco is a subsidiary of Bausch Health Americas, Inc. f/k/a Valeant Pharmaceuticals International, which, directly or indirectly, owns all of the interests in VRX Holdco. Bausch Health Americas, Inc. f/k/a Valeant Pharmaceuticals International is a subsidiary of Biovail International S.a.r.l. and V-BAC Holdings Corp. Biovail International S.a.r.l. and V-BAC Holdings Corp. are subsidiaries of Bausch Health Companies Inc. f/k/a Valeant Pharmaceuticals International, Inc., which, directly or indirectly, owns all of the interests in Biovail International S.a.r.l. and V-BAC Holdings Corp., and no other corporation, entity, or person directly owns 10% or more of the partnership interest in such entities.

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Valeant Pharmaceuticals Intl. **v.** Mylan Pharmaceuticals, Inc.

Case No. 18-2097

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ☐ (appellant) ☐ (respondent) ■ (appellee) ☐ (amicus) ☐ (name of party)

Wyeth LLC

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Wyeth LLC	None	Pfizer Inc.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

William P. Deni, Jr., J. Brugh Lower, Lauren B. Cooper (No longer with the Firm) and Cymetra M. Williams of Gibbons P.C.

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

Valeant Pharmaceuticals International, Inc., et al. v. Mylan Pharmaceuticals, Inc., Civil Action No. 15-08180 (D.N.J.) (Consolidated).

7/6/2018
Date

/s/ Charles H. Chevalier
Signature of counsel

Please Note: All questions must be answered

Charles H. Chevalier
Printed name of counsel

cc: See attached.

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I. STATEMENT OF COUNSEL

1. Based on my professional judgment, I believe the panel decision is contrary to the following decisions(s) of the Supreme Court and this Court:

- *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016), and similar decisions that require a showing of obviousness be made as to the *complete* claimed invention with *all* of its limitations; and relatedly,

- *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186 (Fed. Cir. 2014), *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370 (Fed. Cir. 2019); *Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049 (Fed. Cir. 2017), and similar decisions that do not allow ignoring claim limitations as the mere "inherent or intended result" absent proof of the same.

2. Based on my professional judgment, I believe this appeal separately requires an answer to the following precedent-setting question of exceptional importance:

- Whether this Court's historically narrow principle of *prima facie* obviousness in overlapping range cases should be extended to apply in cases where the prior art differs from the claimed invention in several fundamental and material ways *beyond* the range in question.

/s/ *Bryan C. Diner*
Bryan C. Diner
Attorney for Plaintiffs-Appellees
Valeant Pharmaceuticals International, Inc.,
Salix Pharmaceuticals, Inc., and
Progenics Pharmaceuticals, Inc.

II. POINTS OF LAW AND FACT OVERLOOKED AND MISAPPREHENDED BY THE PANEL

1. The panel legally erred in overlooking the express stability limitation of the pharmaceutical composition claimed in dependent claim 8, improperly concluding its obviousness could be "presumed" and disregarding it as a mere "result."

2. The panel legally erred by misapprehending this Court's narrow principle of *prima facie* obviousness in overlapping range cases, which has never before, and should not now be, expanded to apply in circumstances where the prior art differs from the claimed invention in several fundamental and material ways *beyond* the range in question.

III. INTRODUCTION

Fundamentally, obviousness must be determined as to the *complete* claimed invention, with *all* its limitations. Here, the invention of dependent claim 8 is a pharmaceutical composition comprising three limitations: (i) a specific compound, methylnaltrexone, (ii) a specific pH range, of about 3.0 to about 4.0, and (iii) a never-before-achieved level of storage stability, less than 2% methylnaltrexone degradants for a time period of 24 months at room temperature. The panel's decision to overturn summary judgment of non-obviousness and permit Mylan to continue its unsubstantiated invalidity challenge at trial—absent *any* evidence satisfying the third limitation, or the composition as a whole—threatens settled principles of obviousness in two alarming ways, both requiring correction by this Court.

First, the panel inexplicably "presumed" the storage stability limitation required by dependent claim 8. Slip op. 16. According to the panel's reading of claim 8: "*only* the nature of methylnaltrexone and the pH matter," the stability limitation "can be presumed." Slip op. 3, 16.[1] That is not the law. Neither a party nor or a Court can ignore claim limitations or "presume" their satisfaction—*evidence* is required. And on this record, it is undisputed that *no* prior-art composition, of *any* compound, demonstrated or even came close to claim 8's required stability of less than 2% degradation for 24 months. The panel's "presumed" satisfaction of a

[1] All emphasis is added unless otherwise noted.

fundamental, material claim limitation upsets settled law of obviousness and should not stand.

Second, the panel's decision dangerously expands this Court's narrow jurisprudence regarding routine optimization of overlapping ranges. On a matter of first impression, the panel approved Mylan's "theory of obviousness" whereby "prior art ranges for solutions of structurally and functionally similar compounds that overlap with a claimed range can establish a *prima facie* case of obviousness." Slip op., 11, 14. This extreme theory goes far beyond this Court's precedent, which narrowly recognizes *prima facie* obviousness in certain situations where the prior art is substantively identical to the claimed invention and differs *only* in the range or variable to be optimized. That is far from the case here. Unlike the cited references, or any reasonable combination thereof, instant claim 8 recites a stable pharmaceutical preparation of a *different* compound, at a *different* (albeit overlapping) pH, showing a *different* and never-before-attained level of stability. Given the substantial differences between claim 8 and the prior art, no precedent or policy sanctions a finding of *prima facie* obviousness here. The panel's sudden expansion of the law upends established obviousness principles and all but removes the burden from the challenger to prove invalidity or submit admissible evidence to raise a genuine factual dispute.

Rehearing is required to correct these legal errors.

IV. BACKGROUND

Valeant's U.S. Patent No. 8,552,025 claims stable pharmaceutical preparations of methylnaltrexone, an opioid antagonist. Appx105-128. The '025 patent is listed in the Orange Book for Relistor®, Valeant's subcutaneous methylnaltrexone injection product approved to treat opioid-induced constipation (OIC), a debilitating side-effect of pain-relieving opioid therapy. Appx5009-5010(¶¶2-3). Relistor® was the first FDA-approved drug for the treatment of OIC, and the first FDA-approved methylnaltrexone product. Appx5010-5111(¶4); Appx3371.

Prior to the '025 patent, commercially stable liquid formulations of methylnaltrexone—ones that could be administered subcutaneously and be shelf-stable for long-term storage—were unavailable. Appx119(1:41-42); Appx5010-5011(¶¶4-5). In the early 2000s, Drs. Sanghvi and Boyd developed the first long-term stable injectable methylnaltrexone solution following experimentation with buffering agents, chelating agents, pH, and lyophilization. *E.g.*, Appx123-124(9:7-11:63); Appx126-128(15:41-19:13). The '025 patent is the result of their work. *Id.* Claim 1 recites a stable liquid methylnaltrexone preparation at a pH of between about 3.0 and about 4.0. Appx128(19:25-27). The dependent claims further specify the concentration, excipients, and duration of stability. Appx128(19:28-20:46). Relevant here, the trial court's unchallenged construction of dependent claim 8

requires a specific stability profile: that "the methylnaltrexone degradation products in the preparation do not exceed 2.0% of the total methylnaltrexone present in the preparation and the preparation is suitable for pharmaceutical use when stored for 24 months at room temperature." Appx651.

In 2015, Mylan filed its ANDA seeking approval to market a generic copy of Relistor®, thereby triggering this Hatch-Waxman action. Mylan ultimately stipulated to infringement of claims 8, 21, and 23 of the '025 patent and dropped all defenses to those claims other than obviousness. Appx5374(¶¶3-4). Following expert discovery, Valeant moved for partial summary judgment that Mylan lacked admissible evidence to force a trial on the obviousness of claim 8. Appx2946-2973. Mylan's prior-art compositions taught different compounds (naloxone and naltrexone) at different (albeit overlapping) pH, and fell far short of the stability requirement of less than 2% degradation for 24 months. D.E. 64 at 9-18. Put simply, neither the prior art nor Mylan's expert testimony reached the specific requirements of claim 8. *Id.* In fact, Mylan's evidence proved the opposite: that liquid compositions of naloxone and naltrexone at overlapping pH ranges were unquestionably *unstable* after periods of just six weeks (Bahal, Appx3291-3294) or, at most, 90 days (Appx4117). Thus, even ignoring the differences in both active compound and pH range, there was simply no scientific evidence or explication of

how the deficient stability data in Mylan's references could possibly be extrapolated *8-fold* to reach the requirement of claim 8. D.E. 64 at 25-36.

The district court agreed and granted Valeant's motion. Viewing the evidence most favorably to Mylan, the district court explained that Mylan had failed to raise a triable issue of fact as to obviousness. Appx39-41. Regarding the claimed stability, there was "no evidence that *anyone* had *ever* achieved an injectable pharmaceutical solution stable for 24 months." Appx26. Regarding the claimed pH range, nothing in Mylan's references "indicate[d] that a pH of 3-4 improves the stability of a naloxone solution" or "would have made claim 8 a predictable result." Appx33-34. The district court thus explained that the evidence showed "at best . . . that the skilled artisan, faced with the problem of developing a methylnaltrexone solution with a long shelf-life, would have expected that *experimenting with acid pH might be one of a number of good places to start looking*." Appx39. That evidence simply could not establish a reasonable expectation of success for the specific requirements of claim 8—a methylnaltrexone solution having a pH range of about 3.0 to about 4.0 and not exceeding 2.0% degradants at 24 months—and did not entitle Mylan to trial on the issue. Appx32 ("There is a large gap between this expected result [*some* stability] and claim 8, which is directed to a formulation of methylnaltrexone with a pH between about 3.0 and 4.0 that is stable to storage for 24 months at about room temperature.").

On appeal, this Court reversed and remanded. This decision is marked by two grave legal errors that should be corrected by the panel or the en banc court.

V. ARGUMENT

A. The panel violated binding precedent by "presuming" obviousness of the stability limitation as a mere "result"

It is black-letter law that "in determining obviousness/nonobviousness, an invention must be considered '*as a whole*,' 35 U.S.C. § 103, and claims must be considered *in their entirety*." *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983). "The claims of a patent define the invention," *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005), and a court "may not ignore [a] limitation" in assessing the question of obviousness, *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x. 728, 734 (Fed. Cir. 2019). Thus, a patent challenger who seeks to invalidate a claim for obviousness bears the burden of coming forth with evidence that a person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in "achieving *what is claimed* in the patent-at-issue," as defined by *all* of its limitations. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

The panel's decision violates these fundamental tenets by waiving the requirement for Mylan to show a reasonable expectation of success as to the critical stability limitation of claim 8. The panel's analysis focuses nearly entirely on the

claimed pH range, only addressing the stability limitation of claim 8—Valeant's lead argument on appeal—in the very last paragraph. Slip op. 16. And rather than pointing to any genuine material factual dispute as to reasonable expectation of success on that limitation—because Mylan provided none—the panel simply concludes that "it can be presumed, if the claim is valid, that the stability for up to 24 months must be due to the nature of the compound in the solution and the claimed pH level." *Id.*

The panel's decision that the novel stability requirement of dependent claim 8 "can be presumed" contravenes this Court's precedent. *Intelligent Bio-Sys.*, 821 F.3d at 1367-68. Indeed, a prior precedential decision by this Court expressly *prohibits* that exact legal approach, affirming non-obviousness because "Watson did not identify any prior art references disclosing the critical dissolution limitations of the patented claims, *but merely asserted in a conclusory manner that those limitations would have been obvious or could have been predicted*." *Ferring B.V. v. Waston Labs., Inc.-FL*, 764 F.3d 1401, 1407 (Fed. Cir. 2014). Mylan bears the legal burden to supply evidence that an ordinarily skilled artisan would have had a reasonable expectation in achieving less than 2% methylnaltrexone degradants over a period of 24 months. *Id.*; *Intelligent Bio-Sys.*, 821 F.3d at 1367-68. Yet the detailed analysis and conclusion by the district court—unaddressed by the panel's decision—is that Mylan failed to do so. Appx26 ("[T]here is no evidence that

anyone had *ever* achieved an injectable pharmaceutical solution stable for 24 months."); Appx32 ("Dr. Khan's conclusion falls way short of showing that the invention was a predictable result."); Appx35 ("Defendants begin their discussion by claiming to have evidence which supports their assertion of a reasonable expectation of success, . . . the five pages of discussion that follow do not point it out.").

Nor can the panel decision be saved based on unarticulated ideas of inherency, or that the stability limitation is a mere "result" entitled to no patentable weight. Slip op. 3. First, Mylan did not *argue* those theories in this case, so such questions were completely undeveloped and unripe for adjudication. *United States v. Sineneng-Smith*, 140 S. Ct. 1575, 1579 (2020) (courts "rely on the parties to frame the issues for decision" and "do not, or should not, sally forth each day looking for wrongs to right") (citations omitted).

Second, the opinion is entirely silent as to the law of inherency and patentable weight, or how that law may or may not apply to this case. Thus, to the extent the decision is grounded on those principles, its failure to explain them renders the decision hopelessly confusing and risks dangerous misuse by parties in future cases.

Third, and most significantly, if the panel's decision *does* rest on theories of inherency and patentable weight, it conflicts directly with existing law. To prove a claim invalid for "inherent obviousness," a patent challenger must show that the

limitation at issue is "necessarily present . . . the natural result of the combination of elements explicitly disclosed by the prior art." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014). Similarly, to deny a limitation patentable weight as a mere "intended result," *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001), requires showing that the limitation does not distinguish over the prior art or add a meaningful requirement to the other language of the claim. *E.g.*, *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1375-76 (Fed. Cir. 2019); *Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1060-62 (Fed. Cir. 2017).

Neither is the case here. The claimed stability limitation is not simply a property but a structural component of the claimed formulation—with less than 2% methylnaltrexone *degradants*—that further differentiates the patented formulations from prior art formulations. And clearly from both (i) Mylan's asserted prior-art references, and (ii) the '025 patent specification, the claimed stability is *not* the "necessary result" of the claimed pH range. As to the prior art, it is undisputed that a Bahal naloxone solution at pH 3.2 far exceeded the claimed degradant limit at six weeks, Appx3291(Example 1, Formulation 1); Appx4710(70:2-22); Fawcett's naltrexone solutions at pH of 3.2-3.5 were *not* stable after 90 days, Appx4117, Appx4712(80:11-81:17); and Oshlack's naltrexone preparations were *not* stable after three months, Appx3302-3316; Appx4717-4718(99:18-102:2);

Appx4339(135:11-137:11). Moreover, the '025 patent itself teaches that although the pH range of 3.0-4.0 *can* be enough alone to achieve the claimed stability, Appx122(8:47-58), the use of certain procedures (*e.g.*, the addition of a pH-adjusting base such as sodium hydroxide), will destroy that stability profile, Appx123(10:27-33). Indeed, Mylan's own argument on appeal was that claim 8 does *not* require that the claimed stability be brought about by the pH range alone. *E.g.*, D.E. 56 at 38. [2]

The structural stability limitation of claim 8 is thus *not* the mere "inherent" or "intended" result of the claim and cannot be discounted on those grounds. *PAR*, 773 F.3d at 1195 ("The mere fact that a certain thing *may result* from a given set of circumstances is not sufficient."). *Evidence* of inherency was required, but none was presented. Far from being ignored, this Court has repeatedly recognized the importance of, and relied upon, stability limitations akin to those here in affirming non-obviousness of pharmaceutical compositions. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1354 (Fed. Cir. 2013) (affirming claim to stable compositions nonobvious because, *inter alia*, "the prior art does not teach any composition that exhibits storage stable properties"); *Cumberland Pharm. Inc. v. Mylan Institutional LLC*, 846 F.3d 1213, 1222-23 (Fed. Cir. 2017) (similar); *Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1375-76 (Fed. Cir. 2015) (similar).

[2] Mylan's insinuations that claim 8 lacks § 112 support are both waived and incorrect. *See* Appx5374(¶4) (Mylan expressly dropping such challenges in the district court).

In short, the panel decision violates precedent by "presuming" an express claim limitation in the absence of actual evidence raising a triable factual issue regarding its alleged obviousness. The panel's decision is not justified by unexplained theories of inherency or patentable weight, which were not argued by Mylan, are not provided in the opinion, and in any event are contrary to existing law. Rehearing is warranted to resolve the uncertainty and conflict created by the panel decision and restore the obviousness determination to lawful bounds.

B. The panel's decision expands this Court's historically narrow principle of *prima facie* obviousness in overlapping ranges cases to circumstances entirely inappropriate for such framework

The panel decision requires rehearing for a separate and independent reason—the unjustified and inappropriate expansion of a historically narrow judge-made doctrine regarding *prima facie* obviousness for routine optimization of overlapping ranges. Slip op. at 11 (citing *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003), and related cases). The panel's decision expands this otherwise narrow principle to circumstances far beyond its prior use or sound application, and in doing so threatens a wide range of pharmaceutical composition and other multi-component claims.

In *Peterson*, this Court held that, when "a claimed composition" falls within or overlaps a range disclosed in the prior art, a *prima facie* case of obviousness may exist. 315 F.3d at 1329. The "typical[]" case involves a claim to a pharmaceutical formulation or composition, wherein the *only* pertinent difference between the claim

and the prior art is the range or value of a particular parameter. *Id.*; *see also, e.g.*, *Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc.*, 642 F.3d 1370, 1372 (Fed. Cir. 2011) ("The only physical feature distinguishing the '954 claims from [the prior art] is the amount of temazepam contained in the capsule."); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013) ("[T]he sole dispute between the parties is whether it was obvious to use a 0.3% adapalene composition . . . ."); *Gen. Hosp. Corp. v. Sienna Biopharm., Inc.*, 888 F.3d 1368, 1373-74 (Fed. Cir. 2018) ("[C]laim 74 covers a particular species of the genus set forth in [the prior art]."). In those cases, when the difference between the claim and the prior art is the range or value of a variable to be optimized, a *prima facie* case of obviousness results if the claimed subject matter "is already generally known" and differs only in terms of its optimization. *Peterson*, 315 F.3d at 1330.

That is not this case. Claim 8 recites a pharmaceutical composition comprising a *different* active compound, a *different* (albeit overlapping) pH, and a *different* and previously unattainable level of stability than reported in the asserted prior art. These differences are not trivial. Most significantly, the claimed compound, methylnaltrexone, bears a fundamental structural difference that leads to a profound difference in function. Namely, the prior-art naloxone and naltrexone compounds are *uncharged tertiary amine* compounds—a structure that facilitates their movement across the blood-brain barrier where they act to *reverse* the opioid

effect. Appx4099-4100(¶¶31-34); Appx3044(1:57-67). By contrast, methylnaltrexone is a *positively charged quaternary ammonium* compound—a structure that *prevents* passage across the blood-brain barrier, thereby endowing it with the ability to treat undesirable opioid side-effects *without* interfering with their important pain-relieving action. Appx4041-4043(¶¶45-46); Appx4100(¶¶35-36). This fundamental difference in the claimed compound, accompanied by stability in solution demonstrated *nowhere* in the prior art, is a gap that cannot be bridged by routine optimization.

The panel's decision that these facts nonetheless can support a *prima facie* case of obviousness, slip op. 11-14, requires a new and inappropriate approach of cobbling together the narrow "overlapping ranges" line of caselaw with a separate principle that "skilled artisans can expect structurally similar compounds to have similar properties." Slip op. 12. The panel acknowledges that doing so expands this Court's precedent—"[o]ur previous cases address claims to compounds and their uses," yet concludes that "the principle established in these cases applies more broadly." *Id.* at 13 (citing *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372 (Fed. Cir. 2018) and *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986)). But this Court has never taken such an expansive view, whereby a claim to a new pharmaceutical composition, containing a structurally and functionally *different* active compound exhibiting a hitherto *unachieved* level of stability, could be subject to a theory of

prima facie obviousness because of an overlapping pH range. As Valeant explained in its brief, the two cases on which the panel relies—*Anacor* and *Merck*—are inapposite, as they involved the narrow scenario of shared *pharmacological* activites, based on structurally similar prior-art compounds and evidence linking the structure and function together—circumstances absent here. *See* D.E. 64 at 42-43.

This Court should not accept the panel's new approach, which all but wipes away a patent challenger's burden to establish, *with evidence*, the motivation and reasonable expectation of success to arrive at the complete claimed invention. The panel's decision cannot be squared with established precedent that expressly *rejects* such far-reaching theories of "routine optimization" and "obvious to try" in situations akin to those here. *E.g.*, *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (rejecting obviousness argument based on overlapping prior art, noting the claimed amounts "could and did materially and unpredictably alter the property of the claimed formulation"); *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) ("[O]ne must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result." (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007); *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008) ("The Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try.'").

Moreover, the summary-judgment posture of this case cannot justify the decision. This Court has repeatedly affirmed summary judgment of non-obviousness when, as here, the patent challenger failed to present *evidence* raising a material factual dispute as to obviousness of the complete claimed invention. *See, e.g.*, *Shire LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015); *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1364 (Fed. Cir. 2011); *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). And although the panel expressly allows Valeant on remand to demonstrate non-obviousness (slip op. 14), the decision nonetheless undoubtably will be cited more broadly by zealous litigants who, like Mylan here, seek to invalidate novel pharmaceutical composition and other multi-component claims by seizing upon a single claimed overlapping range while ignoring other fundamental distinctions over the prior art.

VI. CONCLUSION

This petition should be granted by the panel or the en banc court to correct the panel's grave legal errors and restore the district court's grant of summary judgment of non-obviousness.

Dated: June 22, 2020

Respectfully submitted,

/s/ *Bryan C. Diner*

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ADDENDUM

United States Court of Appeals for the Federal Circuit

VALEANT PHARMACEUTICALS INTERNATIONAL, INC., SALIX PHARMACEUTICALS, INC., PROGENICS PHARMACEUTICALS, INC., WYETH LLC, FKA WYETH,
Plaintiffs-Appellees

v.

MYLAN PHARMACEUTICALS INC., MYLAN INC., MYLAN LABORATORIES LIMITED,
Defendants-Appellants

ACTAVIS LLC,
Defendant

2018-2097

Appeal from the United States District Court for the District of New Jersey in Nos. 2:15-cv-08180-SRC-CLW, 2:15-cv-08353-SRC-CLW, 2:16-cv-00035-SRC-CLW, 2:16-cv-00889-SRC-CLW, 2:17-cv-06714-SRC-CLW, Judge Stanley R. Chesler.

Decided: April 8, 2020

BRYAN DINER, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Washington, DC, argued for all plaintiffs-appellees. Plaintiffs-appellees Valeant Pharmaceuticals International, Inc., Salix Pharmaceuticals, Inc., Progenics Pharmaceuticals, Inc. also represented by JUSTIN JAMES HASFORD, CORA RENAE HOLT, ESTHER LIM; JESSICA C. LEBEIS, Boston, MA; CHARLES E. LIPSEY, Reston, VA.

CHARLES H. CHEVALIER, Gibbons P.C., Newark, NJ, for plaintiff-appellee Wyeth LLC. Also represented by JONATHON BRUGH LOWER.

ROBERT FLORENCE, Parker Poe Adams & Bernstein LLP, Atlanta, GA, argued for defendants-appellants. Also represented by MICHEAL L. BINNS, KAREN L. CARROLL.

Before LOURIE, REYNA, and HUGHES, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan Laboratories Ltd. (collectively, "Mylan") appeal from the U.S. District Court for the District of New Jersey's grant of summary judgment that claim 8 of U.S. Patent 8,552,025 ("the '025 patent") is not invalid. *Valeant Pharm. Int'l, Inc. v. Mylan Pharm., Inc.*, No. 2:15-cv-08180 (SRC), 2018 WL 2023537 (D.N.J. May 1, 2018) ("*Decision*"). For the reasons detailed below, we reverse and remand.

BACKGROUND

Valeant owns the '025 patent, which claims stable methylnaltrexone pharmaceutical preparations. According to the '025 patent specification, methylnaltrexone, a quaternary amine opioid antagonist derivative, can be useful for reducing the side effects of opioids but is unstable in aqueous solution. The inventors discovered, however, that when the pH of a methylnaltrexone solution is adjusted,

optimally to between 3.0 and 3.5, the percentage of total degradants drops significantly. '025 patent col. 2 l. 39.

The inventors' preferred manufacturing process for their formulation, as described in Example 2, includes several ingredients acting in concert. Example 2 includes methylnaltrexone, sodium edetate as a chelating agent, sodium citrate and citric acid as buffering agents, and sodium chloride as an isotonicity agent. Each ingredient in the formulation plays its own role. For example, the buffer stabilizes the formulation's pH, which can drop during an autoclaving step, and adding isotonicity agents matches the formulation to the osmotic potential of human extracellular fluids. Chelating agents reduce methylnaltrexone degradation on their own, and the addition of disodium edetate in particular yields an additional, synergistic effect in concert with pH manipulation. The specification thus explains that "manipulating other parameters in concert with pH resulted in stable formulations of methylnaltrexone anywhere in a range from a pH of 2.0 to 6.0." '025 patent col 8. ll. 62–66.

Relevant here are claim 1 and claim 8 of the '025 patent. Claim 8 depends from claim 1, which recites:

> A stable pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation comprises a pH between about 3.0 and about 4.0.

'025 patent col. 19 ll. 25–27. Claim 8 recites "[t]he pharmaceutical preparation of claim 1, wherein the preparation is stable to storage for 24 months at about room temperature." *Id.* col. 19 ll. 44–46. Notably, claim 8 recites the same preparation as claim 1, but with a newly stated result: 24-month stability. Given that there are no limitations indicating any difference between the preparation of claim 1 and claim 8, it is unclear what, if anything, accounts for the added stability limitation. Apparently only the nature of methylnaltrexone and the pH matter. And

there are no limitations in the claim to bring about the stated stability.

The '025 patent is listed in the Orange Book for Relistor®, an injectable drug used to treat constipation as a side effect of taking opioid medication. Mylan filed an Abbreviated New Drug Application ("ANDA") seeking approval from the U.S. Food and Drug Administration to market a generic version of Relistor®, and Valeant responded by bringing suit against Mylan in the District of New Jersey, alleging that Mylan's proposed product would infringe the '025 patent. As relevant here, Mylan ultimately conceded that its ANDA product would infringe claim 8 of the '025 patent but maintained that claim 8 was invalid as obvious over solutions of similar anti-opioids.

The parties stipulated to the construction of claim 8's stability limitation, and the district court did not hold a claim construction hearing. Specifically, the court entered the parties' stipulation that the phrase "the preparation is stable to storage for 24 months at about room temperature" means "the methylnaltrexone degradation products in the preparation do not exceed 2.0% of the total methylnaltrexone present in the preparation and the preparation is suitable for pharmaceutical use when stored for 24 months at room temperature." Stipulation and Order, *Valeant Pharm., Int'l v. Mylan Pharm. Inc.*, 2:15-cv-08180-SRC-CLW (May 30, 2017), ECF No. 148; J.A. 651.

Before the district court, Valeant moved for summary judgment that claim 8 would not have been obvious, and the district court granted Valeant's motion. The court rejected Mylan's expert testimony and cited references as insufficient, largely because the references did not teach methylnaltrexone formulations but instead formulations of similar but different compounds, naloxone and naltrexone. *Decision*, 2018 WL 2023537, at *8. The court also rejected Mylan's theory that the claimed pH range would have been obvious to try. Ultimately, the court held that there was

nothing in the record suggesting that a pH of 3–4, "without added stabilizers," was associated with 24-month stability for injectable pharmaceutical solutions. *Id.* at *10.

Mylan appealed, and we have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a grant of summary judgment under the law of the regional circuit, which in this case is the Third Circuit. *See Charles Mach. Works, Inc. v. Vermeer Mfg. Co.*, 723 F.3d 1376, 1378 (Fed. Cir. 2013) (citing *Grober v. Mako Prods., Inc.*, 686 F.3d 1335, 1344 (Fed. Cir. 2012)). We exercise plenary review over the district court's grant of summary judgment, *Capps v. Mondelez Glob., LLC*, 847 F.3d 144, 151 (3d Cir. 2017) (citing *Seamans v. Temple Univ.*, 744 F.3d 853, 859 (3d Cir. 2014)), reviewing it *de novo*, *Heraeus Med. GmbH v. Esschem, Inc.*, 927 F.3d 727, 733 (3d Cir. 2019) (citing *Faush v. Tuesday Morning, Inc.*, 808 F.3d 208, 215 (3d Cir. 2015)).

Summary judgment is appropriate when the moving party demonstrates that "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322–23 (1986). We construe the evidence in the light most favorable to the nonmovant and draw all reasonable inferences in that party's favor. *Capps*, 847 F.3d at 151 (citing *Prowel v. Wise Bus. Forms, Inc.*, 579 F.3d 285, 286 (3d Cir. 2009)). "Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).

The sole issue in this appeal is obviousness. Obviousness is a question of law, supported by underlying fact questions. *In re Baxter Int'l, Inc.*, 678 F.3d 1357, 1361 (Fed. Cir. 2012). In our obviousness analysis, we consider the

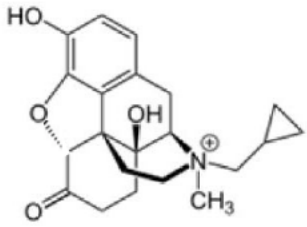
scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and any secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (en banc) ("Objective indicia of nonobviousness must be considered in every case where present.").

Before the district court, Mylan argued that claim 8 would have been obvious in view of three references teaching formulations of either naloxone or naltrexone and in view of two treatises on pharmaceutical formulation. We begin by reviewing those references.

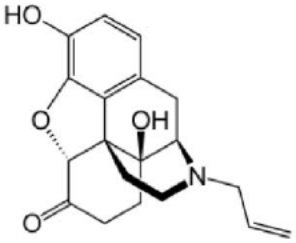
The primary reference at issue here is U.S. Patent 5,866,154 ("Bahal"), entitled "Stabilized Naloxone Formulations" and issued to inventors Surendra Mohan Bahal and Lei-Shu Wu. Bahal teaches stable compositions of naloxone for injection with a pH of 3.0 to 3.5. Similar to the methylnaltrexone formulation described in the '025 patent, the Bahal solutions comprise an opioid antagonist derivative—in this case, naloxone—an acidic or buffer component, a tonicity-adjusting agent, and a stabilizing agent.

Mylan also relied on Oshlack, U.S. Patent Application Publication 2003/0229111, which describes stable naltrexone hydrochloride compositions. Oshlack teaches dissolving a "stabilizer" in solution before adding naltrexone hydrochloride. Stabilizers can be organic acids, and, in certain preferred embodiments, the stabilizer is butylated hydroxytoluene or ascorbic acid. Oshlack ¶ 0051. Thereafter, the pH of the solution may be adjusted to about 3 to about 5, but preferably to about 4. *Id.* ¶ 0054.

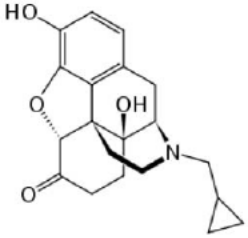
The respective structures of methylnaltrexone, naloxone, and naltrexone are as follows:



Methylnaltrexone



Naloxone



Naltrexone

Fawcett, a journal article about formulations of naltrexone for oral administration, describes decomposition studies on naltrexone in solution at 4, 25 and 70 degrees Celsius over 90 days. J. Paul Fawcett et al., *Formulation and Stability of Naltrexone Oral Liquid for Rapid Withdrawal from Methadone*, 31 ANNALS OF PHARMACOTHERAPY, 1291–95 (1997). At 25 degrees, decomposition was not significant, but at 70 degrees, the color of the naltrexone turned brown, indicating physical instability. The concentration of naltrexone dwindled over time, and the pH of the formulations at all temperatures fell from 3.5 to 3.2.

Gibson, a pharmaceutical development treatise, recommends target pH ranges of 3 to 11 for intramuscular formulations and 3 to 6 for subcutaneous administration. Joanne Broadhead, *Parenteral Dosage Forms*, *in* PHARMACEUTICAL PREFORMULATION AND FORMULATION 331, 333 (Mark Gibson ed., 2001); J.A. 3225. Gibson

explains that many products are formulated at a slightly acidic pH because of solubility or stability considerations and that the majority of licensed products have a pH between 3 and 9. According to Gibson, more acidic pH can cause phlebitis and pain, while more basic pH can cause tissue necrosis.

Similarly, another pharmaceutical treatise, Remington, teaches that drugs with amide or ester linkages are prone to hydrolysis. Remington explains that many hydrolytic reactions are catalyzed by hydronium and hydroxyl ions, so pH is a relevant consideration in determining the rate of decomposition. 1 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 643 (Alfonso R. Gennaro et al. eds., 19th ed. 1995); J.A. 3255. According to Remington, "[t]he pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction," but, "[i]n general, hydroxyl ions have the stronger effect." Thus, Remington concludes, the minimum reactivity "is often found between pH 3 and 4." *Id.*

Relying on these references, Mylan argued that a person of skill in the art would have been motivated to prepare and would have arrived at the preparation of claim 8 via routine optimization of pH. Bahal, Oshlack, and Fawcett each taught pH ranges that overlapped with the "about 3 to about 4" range in claim 8, but those references detailed formulations of naloxone and naltrexone. In Mylan's view, however, the references still established a prima facie case of obviousness because naloxone and naltrexone were structurally and functionally similar to methylnaltrexone. Mylan also argued that the pH range in the claim would have been obvious to try.

The district court disagreed, rejecting Mylan's arguments about Bahal, Oshlack, and Fawcett because none of the references taught methylnaltrexone formulations. In the court's view, overlapping ranges only establish a prima facie case of obviousness when the only difference between

the prior art is the "range or value of a particular variable." *Decision*, 2018 WL 2023537, at *4.

The district court then turned to what it deemed to be Mylan's main argument—that a pH range of 3 to 4 would have been obvious to try. The court expressly rejected Mylan's view that the range was just one of a finite number of options between pH 3 and 7 that a person of skill would try, holding that "given any two unequal numbers, the quantity of number ranges falling between the two is infinite, not finite," adding that this conclusion was one of "basic math." *Decision*, 2018 WL 2023537, at *5. Mylan cited Gibson and testimony from two experts that adjusting pH could improve stability, but the court rejected this evidence because, in its view, the evidence did not support that "adjusting pH would be the *first* variable formulators would consider to improve stability." *Id.*

Next, the court rejected Mylan's assertion that long-term stability of methylnaltrexone was a predictable result of arriving at a pH range of 3 to 4. The court faulted the expert report of Dr. Khan, Mylan's expert, because he stated that a person of skill would have expected "stable formulations" of methylnaltrexone at an acidic pH. The court held that there was a "large gap" between this testimony and the specific claimed pH range of 3 to 4 with its claimed stability profile of 24 months. *Id.* at *7.

In the remainder of its analysis, the district court detailed how the prior art references and expert testimony of record failed to establish that methylnaltrexone could be stabilized based on *pH alone*. The court expressly rejected Bahal and Oshlack for their reliance on stabilizers in addition to pH manipulation, holding that neither reference taught a formulation "without added stabilizers." *Id.* at *7–9. The court recognized that the prior art suggested that pH was "generally important in formulating pharmaceuticals" and could "have an effect on stability," but, in its view, the art did not contemplate an injectable solution

"made stable over the long term by pH alone." *Id.* at *10. After stating that the art recognized that adjusting pH was only "one dart among a number of others," the court granted Valeant's motion for summary judgment that claim 8 would not have been obvious. *Id.* at *10–11.

In this appeal, Mylan argues that the district court erred in at least two respects: (1) by failing to hold that Mylan established a prima facie case that claim 8 would have been obvious because the pH range in the claim overlaps with pH ranges in the prior art for similar compounds and (2) by resolving disputed fact issues at summary judgment. We address each argument in turn.

I

Mylan cites three prior art references involving different compounds, but each discloses formulations with pH ranges that overlap with the range recited in claim 8, pH between about 3 and about 4. Specifically, Bahal teaches a naloxone composition with a pH of 3 to 3.5, Oshlack teaches a naltrexone composition with a pH of about 3 to about 5 and about 4, and Fawcett discloses a naltrexone formulation with a pH of 3.5 that fell to 3.2 over 90 days. In Mylan's view, these references establish a prima facie case of obviousness because the pH ranges they teach overlap with those in claim 8. While no reference contemplates methylnaltrexone specifically, Mylan submits that methylnaltrexone bears significant structural and functional similarity to both naloxone and naltrexone such that a person of skill in the art would seek to use prior disclosed pHs for naloxone and naltrexone when formulating solutions of methylnaltrexone.

Valeant responds that overlapping ranges for different chemical compounds that fail to meet claim 8's stability requirement do not establish obviousness. According to Valeant, the structural and functional similarities of the compounds are not relevant because claim 8 recites a solution of methylnaltrexone with a stability profile

unrecognized and unattained in the prior art. Nevertheless, Valeant submits, methylnaltrexone, naloxone, and naltrexone function differently because of their structural differences, and nothing about the shared function of the drugs is relevant to their stability in solution.

We agree with Mylan that the record supports a prima facie case of obviousness here. In *Peterson*, this court recognized that "[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (citing *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997)); *In re Woodruff*, 919 F.2d 1575, 1578 (CCPA 1990); *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974)). At issue in *Peterson* was a claim to a nickel-base single-crystal superalloy used in the manufacture of turbine engines. The claimed composition included a relatively small amount of rhenium—about 1 to 3 percent. The prior art of record taught compositions with 0 to 7 percent rhenium, an overlapping range within which the narrower, claimed range fell. We explained that "[s]electing a narrow range from *within* a somewhat broader range disclosed in a prior art reference is no less obvious than identifying a range that simply *overlaps* a disclosed range." *Peterson*, 315 F.3d at 1329–30. We thus held that the overlapping ranges were sufficient to establish a prima facie case of obviousness, shifting the burden to the patentee to show that the invention would not have been obvious.

Here, the pH range recited in claim 8 clearly overlaps with the pH range in the record art, but none of the references disclose the same drug as the one claimed. We are thus presented with the question whether prior art ranges for solutions of structurally and functionally similar compounds that overlap with a claimed range can establish a prima facie case of obviousness. We conclude that they can and, in this case, do.

We have held that, for chemical compound claims, a prima facie case of obviousness "frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010) (citing *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). Our case law reflects an understanding that skilled artisans can expect structurally similar compounds to have similar properties. *See, e.g.*, *Dillon*, 919 F.2d at 692 ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness . . . ."); *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds."). We have also recognized that an obviousness analysis can rely on prior art compounds with similar pharmacological utility in addition to structural similarity. *See, e.g.*, *In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (holding that a person of skill in the art would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans because of the drugs' close structural similarity and similar use); *Application of Payne*, 606 F.2d 303, 314 (CCPA 1979) ("Because of the close structural similarity between the claimed compounds at issue here and the compounds [in the prior art], and because those prior art compounds possess pesticidal activity, we conclude that the required motivation is present here." (citing *In re Wood*, 582 F.2d 638, 641 (CCPA 1978)); *Application of Rosselet*, 347 F.2d 847, 850 (CCPA 1965) ("[A]ppellants have failed to present adequate evidence to overcome a prima facie showing of obviousness by reason of the admitted 'gross structural similarities' of the art compounds, coupled with the fact those compounds are shown to have utility in the same area of pharmacological activity.").

Our previous cases address claims to compounds and their uses. But the principle established in these cases applies more broadly: a person of skill in the art can expect that compounds with common properties are likely to share other related properties as well. *See Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384 (Fed. Cir. 2018) ("Where the patent is directed to a new treatment using a known compound, it is reasonable to assume that similar compounds that share certain common properties are apt to share other related properties as well." (citing *Merck*, 800 F.2d at 1096)). When compounds share significant structural and functional similarity, those compounds are likely to share other properties, including optimal formulation for long-term stability.

Here, the art teaches stable formulations of naloxone, naltrexone, and methylnaltrexone. All three compounds are well-known opioid antagonists that operate by binding to the body's opioid receptors without activating them. Each is an oxymorphone derivative, and the group members have remarkably similar structures, as indicated earlier. The only structural difference between these three molecules is the identity of the functional group attached to the nitrogen atom. Naloxone is a neutral tertiary amine. Naltrexone, also a neutral tertiary amine, has a cyclopropylmethyl group attached to the nitrogen. Methylnaltrexone, a derivative of naltrexone, is a quaternary ammonium salt and has both a cyclopropylmethyl group and a methyl group attached to its nitrogen with a positive charge. Because of the strong structural and functional similarity between the molecules, a person of skill could expect similar stability of the molecules at similar pH ranges in solution. The district court erred by rejecting this inference as a matter of law at the summary judgment stage.

Because these three molecules bear significant structural and functionality similarity, and because the prior art of record teaches pH ranges that overlap with the pH range recited in claim 8, Mylan has at least raised a prima

facie case of obviousness sufficient to survive summary judgment.

Our holding should not be misconstrued to mean that molecules with similar structure and similar function can always be expected to exhibit similar properties for formulation. Indeed, when this case is tried to a factfinder, the factfinder should consider whether Valeant has rebutted Mylan's prima facie case, by, for example, establishing that the claimed pH range is critical or that the quaternary nitrogen results in unexpected beneficial properties. *See, e.g.*, *Geisler*, 116 F.3d at 1469; *Woodruff*, 919 F.2d at 1578. Valeant may also attempt to rebut Mylan's case by showing that the prior art teaches away from the claimed invention in any respect. *Peterson*, 315 F.3d at 1331 (citing *Geisler*, 116 F.3d at 1469). Whether methylnaltrexone's structural similarity in an overlapping range of pH in solution is sufficient to yield a prima facie case of obviousness depends on the facts of record. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) ("Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts."). Contrary to the district court's view in this case, however, such a theory of obviousness is not defective as a matter of law, and summary judgment to that effect was granted in error.

II

Next, we address Mylan's argument that there were factual disputes precluding summary judgment. Many of Mylan's arguments have been adequately addressed by our analysis above. Mylan raises a significant concern, however, with the district court's obvious-to-try analysis. In evaluating Mylan's obvious-to-try argument, the district court held that there was not a finite number of options between pH ranges falling between 3 and 7. The court held that, as a matter of "basic math," "given any two unequal numbers, the quantity of number ranges falling between the two is infinite, not finite." *Decision*, 2018 WL 2023537,

at *5. The court also rejected Mylan's citations of expert testimony and prior art references because none of the references identified pH as the "first variable" that an experienced formulator would consider and because Mylan's expert concluded that a person of skill would have expected only "stable formulations," not formulations stable for 24 months at room temperature. *Id.* at *6–7.

In Mylan's view, the district court disregarded Mylan's obvious-to-try evidence because the pH ranges taught in the prior art were not sufficiently narrow. Mylan submits that the adequacy of a prior art range is a classic question of fact and that the district court imposed a heightened predictability requirement.

Valeant does not appear to defend the district court's "basic math" reasoning and, respectfully, we disagree with the court's view of basic math. Instead, Valeant responds that a pH range of 3 to 4 would not have been obvious to try because the asserted prior art did not disclose a formulation exhibiting 24-month stability and because Mylan's experts did not explain why such stability would have been expected.

We agree with Mylan that the district court's obvious-to-try analysis is inconsistent with precedent. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). If one of these predictable solutions leads to the anticipated success, the combination was obvious to try. *Id.*

The bounded range of pH 3 to 4 presents a finite number of narrower pH ranges for a skilled artisan to try. As a matter of math, there may be an infinite potential number of ranges within the range 3 to 4, but only if the realities of pH values (and the limitations of commercially available pH meters) are ignored. But on this record, there

is no indication that pH is measured to any significant figure beyond two digits. And in our view of basic math and based on the record, there is only one significant figure after the decimal point, in which case the range of pH variables is ten, or, if one considers two significant figures after the decimal point, one hundred, not an infinity.

The district court rejected record evidence because no reference listed pH as the "first variable" that an artisan would manipulate. But there is no requirement that for a variable to be obvious to try, it must be the first variable a person of skill would alter. And as to the stability limitation, a factfinder could draw the inference from this record that trying a pH of 3–4 would lead to a methylnaltrexone formulation stable at room temperature. Absolute predictability that the proposed pH range would yield the exact stability parameters in the claim is not required. Moreover, it is important to note that pH is in fact the only variable in claim 8, not one of many variables that can be experimented with. And, lacking anything in the claim that is a stabilizer, it can be presumed, if the claim is valid, that the stability for up to 24 months must be due to the nature of the compound in the solution and the claimed pH level. Thus, the district court's grant of summary judgment on Mylan's obvious-to-try theory was in error.

CONCLUSION

We have considered the parties' remaining arguments but find them unpersuasive. In light of the foregoing, we reverse the district court's grant of summary judgment that claim 8 would not have been obvious and remand this case for further proceedings consistent with this opinion.

REVERSED AND REMANDED

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME AND TYPEFACE REQUIREMENTS

This petition complies with the type-style and type-volume requirements of Federal Rules of Appellate Procedure 32(a) and 35(b)(2) and Federal Circuit Rules 32(b) and 35(c)(2). This petition contains 3,841 words, as determined by the word-count function of Microsoft Word, excluding the parts of the brief exempted by Federal Circuit Rule 35(c)(2). This brief has been prepared in a proportionally spaced typeface using Microsoft Word in Times New Roman 14 point font.

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Respectfully submitted,

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